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CHELATION-CONTROLLED NUCLEOPHILIC ADDITIONS.

1. A HIGHLY EFFECTIVE SYSTEM FOR ASYMMETRIC INDUCTION IN  
THE REACTION OF ORGANOMETALLICS WITH  $\alpha$ -ALKOXYKETONES.<sup>1</sup>

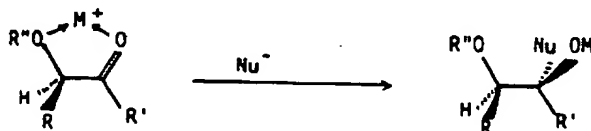
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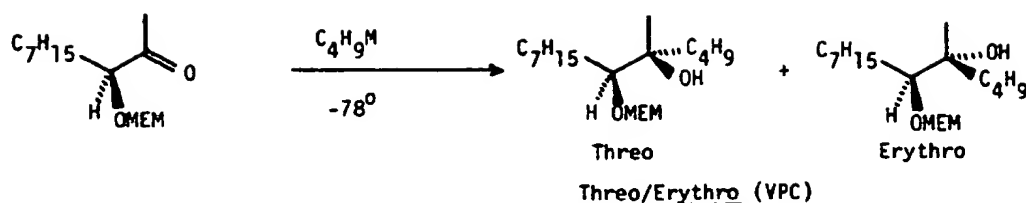
**SUMMARY:** An optimum reaction system is described for the highly stereoselective addition of carbanionic nucleophiles to chiral  $\alpha$ -alkoxyketones. A variety of oxygen protecting groups are acceptable and allow chelation-controlled  $\alpha$ -asymmetric induction with diastereomeric product ratios ranging from 50-200:1.

The addition reaction of carbon nucleophiles with carbonyl compounds is one of the most powerful construction methods available to synthetic organic chemistry. It is particularly useful for the preparation of complex, highly-oxygenated materials, and in fact our recent synthesis<sup>2</sup> of the polyether antibiotic monensin relied exclusively on this operation for the formation of carbon-carbon bonds. There is however one potentially problematic aspect of the reaction which requires special consideration as applied to most syntheses. That problem is  $\alpha$ -induction. When nucleophiles are added to chiral aldehydes or ketones, undesirable mixtures of diastereomers often result.<sup>3</sup> As part of a synthetic program directed toward certain polyether antibiotics, we have examined in some detail the reaction of various organometallics with aldehydes and ketones having  $\alpha$ -asymmetric centers and either  $\alpha$  or  $\beta$  oxygen substituents. We report here our results with acyclic  $\alpha$ -alkoxyketones which show that consistently high values of  $\alpha$ -induction may be obtained using Grignard reagents in tetrahydrofuran.

In pioneering work in the area, Cram and coworkers examined a variety of  $\alpha$ -alkoxyketones and found that the major products were nicely rationalized by a cyclic transition state in which the nucleophile added to the less hindered face of a chelated carbonyl.<sup>4</sup> Unfortunately,



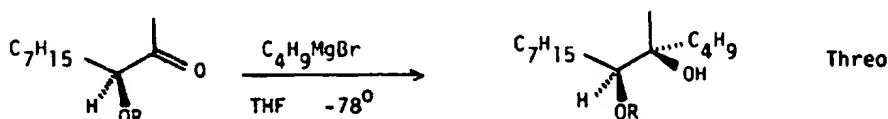
the extent of  $\alpha$ -induction was not particularly high, ranging between 2:1 and 9:1. Since that time, scattered reports of significantly higher  $\alpha$ -induction have been accumulating for compounds where the  $\alpha$ -alkoxy substituent is a cyclic ether oxygen.<sup>5</sup> In order to evaluate the reaction as a highly stereoselective route to vicinal diols, we have studied the reaction of *n*-butyllithium and *n*-butylmagnesium bromide with the methoxyethoxymethyl (MEM)<sup>6</sup> ether of 3-hydroxy-2-decanone.



|  | M = Li | M = MgBr |
|--|--------|----------|
| Solvent = C <sub>5</sub> H <sub>12</sub> | 2      | 9        |
| = CH <sub>2</sub> Cl <sub>2</sub>        | 3      | 14       |
| = Et <sub>2</sub> O                      | 1      | 9        |
| = THF                                    | .7     | >100     |

As shown by the data above, the Grignard reagent in tetrahydrofuran gives extremely high stereoselectivity for the threo product (>95% isolated yield). The stereochemistry of the addition was verified by comparison with authentic material and is that predicted by the cyclic chelate model.

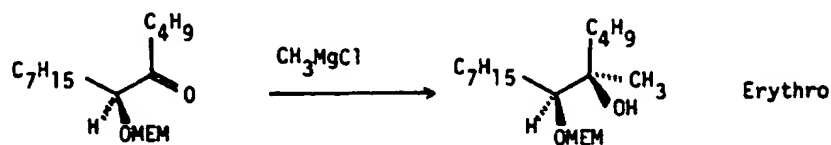
To establish the generality of the reaction, we have examined a number of protected  $\alpha$ -ketols and find that considerable substrate variation can be tolerated without loss of stereochemical control. For example, the listing below shows that many common hydroxyl protecting groups are suitable for the addition although several of the groups (-MEM, methylthiomethyl and methoxymethyl) could not be removed without conversion to a cyclic methylenedioxy compound. Thus benzyl, benzyloxymethyl or furfurylmethyl are preferred if the free diol is desired.



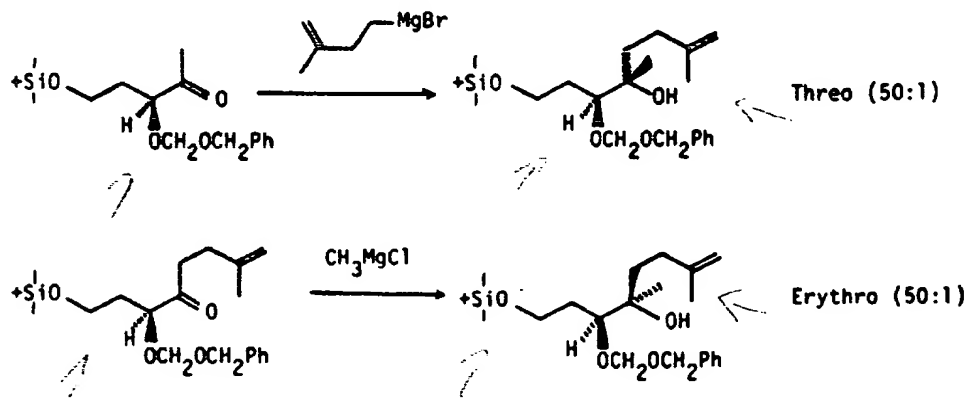
|  | Threo/Erythro         |
|--|-----------------------|
| R = -MEM, -MOM, -MTM, -CH <sub>2</sub> - | >100 (VPC)            |
| = -CH <sub>2</sub> Ph                    | 200 (HPLC)            |
| = -CH <sub>2</sub> OCH <sub>2</sub> Ph   | 100 (HPLC)            |
| = -THP                                   | 3 (HPLC) <sup>7</sup> |

The relatively poor selectivity found with -THP is noteworthy and may be general for acyclic  $\alpha$ -ketols protected by groups which hinder the protected oxygen. In the system at hand, molecular models suggest that one of the two diastereomeric tetrahydropyranyl ethers may disfavor the intermediate cyclic chelate and thus degrade the stereoselectivity otherwise associated with these reactions. This proposal receives some support from Grignard additions to the separated THP diastereomers. Thus the major tetrahydropyranyl ether gives a 2.5:1 threo:erythro mixture while the minor diastereomer adds butylmagnesium bromide with  $>10:1$ <sup>8</sup> stereoselectivity for threo.

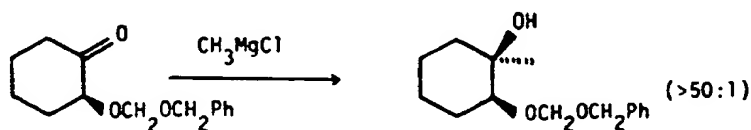
Monoprotected diols of the opposite stereochemistry are available by interchange of Grignard and ketone substituents. For example, the addition of methylmagnesium chloride (THF,  $-78^{\circ}\text{C}$ ) to the butyl ketone below affords the erythro diol derivative (erythro:threo  $>100:1$ ).



More complex, optically active diols are also readily constructed with high stereoselectivity and without racemization<sup>9</sup> as illustrated by the following conversions:<sup>10</sup>



Finally it should be added that the addition does not appear to be restricted to acyclic  $\alpha$ -alkoxyketones since the addition of methylmagnesium bromide to benzyloxymethyl-protected 2-hydroxycyclohexanone gave the protected cis-diol stereospecifically.



In conclusion tetrahydrofuran solutions of Grignard reagents add with very high stereoselectivity to chiral  $\alpha$ -alkoxyketones. Although the metal and the solvent are of major importance in determining the extent of  $\alpha$ -induction, other experiments indicate that modest improvements in stereocontrol may be further obtained by the addition of several equivalents of magnesium halide to the Grignard reagent and through the use of alkylmagnesium chlorides in place of the corresponding bromides or iodides. Interestingly the reaction shows little temperature dependence giving only slightly higher  $\alpha$ -induction at  $-78^{\circ}\text{C}$  than at room temperature.<sup>11</sup>

#### References and Notes:

1. This work was described in part at the Sixth International Symposium on Synthesis in Organic Chemistry in Cambridge, England, on July 25, 1979.
2. D.B. Collum, J.H. McDonald and W.C. Still, *J. Am. Chem. Soc.*, submitted.
3. Reviews: D.J. Morrison and H.S. Mosher, "Asymmetric Reactions," Prentice Hall, Englewood Cliffs, NJ, 1971; D.R. Boyd and M.A. McKerverey, *Quart. Rev. Chem. Soc.*, **22**, 95 (1968); T.D. Inch, *Synthesis*, **2**, 466 (1970); S. Yamada and K. Koga, "Selective Organic Transformations," Vol. 1, B.S. Thyagarajan, Ed., Wiley-Interscience, New York, NY, 1970.
4. D.J. Cram and K.R. Kopecky, *J. Am. Chem. Soc.*, **81**, 2748 (1959).
5. M.L. Wolfrom and S. Hanessian, *J. Org. Chem.*, **27**, 1800 (1962); T.D. Inch, *Carbohydr. Res.*, **5**, 45 (1967); R. Meric and J.-P. Vigneron, *Bull. Soc. Chim. Fr.*, 327 (1973); S. Hanessian, G. Rancourt and Y. Guindon, *Can. J. Chem.*, **56**, 1843 (1978); T. Nakati and Y. Kishi, *Tetrahedron Lett.*, 2745 (1978); E. L. Eliel, J.K. Koskimies and B. Lohri, *J. Am. Chem. Soc.*, **100**, 1616 (1978); E.L. Eliel and W.J. Frazee, *J. Org. Chem.*, **44**, 3598 (1979).
6. E.J. Corey, J.L. Gras and P. Ulrich, *Tetrahedron Lett.*, 809 (1976).
7. Analysis was conducted after benzylation and removal of THP.
8. The actual stereoselectivity is probably much greater than 10:1 since the two THP diastereomers could not be completely separated.
9. HPLC analysis of the (-)-MTPA esters of the deprotected (Li/NH<sub>2</sub>) products showed homogeneous material under conditions which cleanly resolved the corresponding esters derived from racemic material.
10. These experiments were carried out by David B. Collum.
11. This work was supported by NSF grant CHE78-01769.

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